Cannabinoids, a new hope for cancer therapy?

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MUTATIONS | UNCONTROLLED CELL PROLIFERATION | ANGIOGENESIS | METASTASIS

TUMOR PROGRESSION

ONCOLOGIC PAIN | SIDE EFFECTS

Hair loss
Anemia
Constipation/Diarrhea
Pain (bone, joint, chest, muscle)
Toxicity (heart, liver, kidneys)
Lack of appetite, nausea, vomiting

ANTI-CANCER THERAPIES
MUTATIONS
UNCONTROLLED CELL PROLIFERATION
ANGIOGENESIS
METASTASIS
MUTATIONS

TUMOR PROGRESSION
ONCOLOGIC PAIN
SIDE EFFECTS

CANNABINOIDS

Hair loss
Anemia
Constipation/Diarrhea
Pain (bone, joint, chest, muscle)
Toxicity (heart, liver, kidneys)
Lack of appetite, nausea, vomiting

ANTI-CANCER THERAPIES
1. THEY MUST WORK

They must kill cancer cells/block cancer cell propagation

There must be targets in human patients

2. THEY MUST BE SAFE

They must not produce toxic effects on non-cancer cells

They must not produce side effects
1. DO CANNABINOIDS WORK?

2. ARE CANNABINOIDS SAFE?
1. DO CANNABINOIDS WORK as antitumor agents?

GLIOBLASTOMA MULTIFORME

Treatments: Tumor resection + Radiotherapy + Chemotherapy (Temozolomide)

Life expectancy of patients with GBM: 14 months after diagnosis
1. DO CANNABINOIDs WORK as antitumor agents?
1. DO CANNABINOIDs WORK as antitumor agents?

Galve-Roperh et al., Nature Medicine 2000
1. DO CANNABINOIDs WORK as antitumor agents?

UNsolved issues: Innate and acquired RESISTANCE to anticancer drugs
METASTASIS in the central nervous system
Anticancer drug-associated SIDE EFFECTS
1. **DO CANNABINOIDs WORK as antitumor agents?**

**THE MMTV-neu MOUSE: A CLINICALLY RELEVANT MODEL OF HER2-POSITIVE METASTATIC BREAST CANCER**

- **LAB RESEARCH**

- **MMTV-neu**

- **Tumour-free animals (%):**
  - n=39
  - $t_{50} = 252$

- **Age (Days):**
  - 0 to 600

- **Tumour (appearance of the first tumour):**
  - $t_0$

- **20 mg/Kg THC Peritumourally Twice a week**

- **90 days (end of treatment)**

- **Lung metastases**
1. DO CANNABINOIDs WORK as antitumor agents?

THC REDUCES TUMOUR GROWTH

<table>
<thead>
<tr>
<th>Time of treatment (days)</th>
<th>Tumour volume (mm$^3$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>200</td>
</tr>
<tr>
<td>30</td>
<td>300</td>
</tr>
<tr>
<td>40</td>
<td>400</td>
</tr>
<tr>
<td>50</td>
<td>500</td>
</tr>
<tr>
<td>60</td>
<td>600</td>
</tr>
<tr>
<td>70</td>
<td>700</td>
</tr>
</tbody>
</table>

Veh (n=15)

THC (n=6)

THC REDUCES TUMOUR GENERATION

<table>
<thead>
<tr>
<th>Tumors/animal</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n=12)</td>
<td>25%</td>
<td>8%</td>
<td>25%</td>
<td>41%</td>
</tr>
<tr>
<td>THC (n=6)</td>
<td>50%</td>
<td>17%</td>
<td>33%</td>
<td>0%</td>
</tr>
</tbody>
</table>

THC REDUCES LUNG METASTASES

Caffarel et al., Mol Cancer 2010
1. DO CANNABINOIDS WORK as antitumor agents?

Andradas, Pérez-Gómez et al., Unpublished
1. DO CANNABINOIDS WORK as antitumor agents?

**LAB RESEARCH**

**BT474**

**BT474 cells** (5x10^6)

**ORAL ADMINISTRATION**

**VEHICLE** (sesame oil)

**THC** (45mg/Kg/3 days a week)

Andradas, Pérez-Gómez et al., Unpublished
LAB RESEARCH

1. DO CANNABINOIDs WORK as antitumor agents?

Andradas, Pérez-Gómez et al., Unpublished
1. DO CANNABINOID WORK as antitumor agents?

<table>
<thead>
<tr>
<th>Hormone receptor status</th>
<th>CB₂ staining</th>
<th>n</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>117 (23%)</td>
<td>191</td>
<td>135</td>
<td>61</td>
<td></td>
<td></td>
<td>0.655</td>
</tr>
<tr>
<td>Negative</td>
<td>24 (21%)</td>
<td>41</td>
<td>38</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6x10⁻⁷</td>
</tr>
<tr>
<td>Positive</td>
<td>3 (3%)</td>
<td>29</td>
<td>39</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>86 (24%)</td>
<td>141</td>
<td>94</td>
<td>39</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple negative status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.138</td>
</tr>
<tr>
<td>Positive</td>
<td>13 (28%)</td>
<td>20</td>
<td>12</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>76 (19%)</td>
<td>150</td>
<td>121</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
1. DO CANNABINOIDS WORK?

2. ARE CANNABINOIDS SAFE?
LAB RESEARCH

2. ARE CANNABINIODS SAFE?

EFFECT PRODUCED BY ACTIVATION OF CB2

MMTV-neu mouse

N202.1A CELLS

Caffarel et al., Mol Cancer 2010
1. DO CANNABINOIDS WORK as antitumor agents?

**EFFECT PRODUCED BY CBD**

Human cells

[Graph showing cell viability (% vs control) for different cannabinoid concentrations (0.5, 1, 1.5 µM) and cannabinoids (Control, THC, CBD). The graph indicates the effect of CBD on cell viability.]

Andradas, Pérez-Gómez et al., Unpublished
1. DO CANNABINOIDS WORK as antitumor agents?

**EFFECT PRODUCED BY CBD**

**BT474**

Human cells

**LAB RESEARCH**

- Veh
- THC 45mg/Kg
- CBD 45mg/Kg

**Tumour volume (mm³)**

- **Time (days)**
  - 0
  - 2
  - 4
  - 6
  - 8
  - 10
  - 12
  - 14
  - 16
  - 18
  - 20
  - 22
  - 24
  - 26
  - 28
  - 30

Andradas, Pérez-Gómez et al., Unpublished
ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

Explore 256,651 research studies in all 50 states and in 201 countries.

ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

IMPORTANT: Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

Before participating in a study, talk to your healthcare provider and learn about the risks and potential benefits.

Sativex: 371 trials completed
Marinol: 114 trials completed
CBD: 52 trials completed
1. DO CANNABINOIDS WORK?
   ✓ YES (in preclinical models of cancer)

2. ARE CANNABINOIDS SAFE?
   ✓ YES

WHAT DO WE DO NEXT?
A pilot clinical study of $\Delta^9$-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme

Primary endpoint
• Safety and life quality

Secondary endpoints
• Survival
• Tumor growth
• Effect on tumor markers
GBM DIAGNOSIS

1ST SURGERY

RADIOThERAPY ± CHEMOTHERAPY

RECURRENCE

2ND SURGERY: CATHETER INSERTION
PRE-TREATMENT BIOPSIES

THC TREATMENT

POST-TREATMENT BIOPSIES

DECEASE

THE FIRST PILOT CLINICAL STUDY

EXPERIMENTAL STAGE
1. THC produced NO PSYCHOTROPIC EFFECTS
2. THC REDUCED TUMOR GROWTH in some patients
3. THC INCREASED LENGTH OF SURVIVAL in some patients
4. THC modulates the SAME MOLECULAR MECHANISMS as in preclinical models
A Safety Study of Sativex Compared With Placebo (Both With Dose-intense Temozolomide) in Recurrent Glioblastoma Patients

**Primary endpoint**
- Safety in patients receiving (Sativex + TMZ) vs (Placebo + TMZ)

**Secondary endpoints**
- Progression-free survival at 6 months
- Overall survival

Estimated Enrollment: 20
Study Start Date: September 2014
Estimated Study Completion Date: October 2015
Estimated Primary Completion Date: October 2015 (Final data collection date for primary outcome measure)
CONCLUSIONS

PHYTOCANNABINOIDS:

• **WORK**

• **ARE SAFE:** Effects on transformed cells

  Effects mediated by CB2

  Effects produced by CBD

  Clinical trials

• **HAVE ADDITIONAL ADVANTAGES:** Analgesic, orexigenic, antiemetic

NEXT STEPS

- More preclinical data (mechanism of action, combinations with other chemotherapeutic drugs, etc)

- MORE CLINICAL TRIALS
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Biodonostia
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Angela Araujo
Andrea Abaurrea

Oncology team

Cancer patients

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